NOVARTIS

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July 6, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Novartis Comments on FDA Draft Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

Docket No. 2004D-0189

Dear Sir/Madame:

Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ more than 78,000 people and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer and arthritis.

Novartis and the FDA share a mutual interest in making safer and more effective products available to patients as rapidly as possible, as well as ensuring their appropriate use and minimizing the occurrence of preventable adverse events. As one of the world's largest pharmaceutical companies, Novartis commits extensive resources to developing drugs and bringing them to market. It is essential that FDA ensure that its policies and expectations regarding risk management are clear and transparent to all stakeholders, and that the standards are consistently applied. We appreciate the opportunity to provide comments on the draft guidance documents.

General Comments

Novartis positively acknowledges FDA's efforts to incorporate public comments on the previous Concept Paper into this Draft Guidance. We strongly support FDA's position that it is not possible to detect all safety concerns during clinical trials and that for most products, routine pharmacovigilance and FDA-approved professional labeling are sufficient for post-marketing risk assessment and risk minimization. In addition, we agree that dialogue and collaboration between the Agency and sponsor in the planning and follow-up of pharmacovigilance and pharmacoepidemiology activities is an essential component of understanding and managing the risks associated with medicines.

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While we believe the Draft Guidance has clarified and restated several important aspects presented in the Concept Paper, there remain issues of concern that we feel have not adequately addressed, including:

- Definitions – Terms are not in line with international harmonization efforts or have not been adequately defined.
- Role and usefulness of data mining techniques for signal detection
- Lack of consensus around international harmonization initiatives
- Assessment of causality in individual safety reports

These are described in more detail below, followed by our comments on specific sections of the draft document.

Definitions

Pharmacovigilance: The definition of pharmacovigilance presented in the draft guidance (line 115) is not fully harmonized with the definition in the ICH E2E draft guidance on Pharmacovigilance Planning. The ICH E2E document, agreed to by FDA, utilizes the WHO definition, i.e. "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem." In contrast, the FDA definition ("all observational (nonrandomized) postapproval scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events") is limited to post-approval activities. In addition, although both the FDA definition and the ICH/WHO definition encompass pharmacoepidemiologic studies, the FDA definition specifically limits these to pharmacoepidemiologic *safety* studies. As a partner to the ICH process, we strongly urge FDA to adopt the internationally accepted definition of pharmacovigilance in this guidance document, and that the term be used consistently throughout the document.

Signal: Novartis recommends that FDA include a definition of "signal" in the guidance document, as this term is used frequently throughout the draft document, but not always in a consistent manner. For example, in line 121, there is an implied definition that a signal is "an excess...of adverse events associated with a product's use". In lines 361 – 384 there is also a wide-ranging list of "safety signals that warrant further investigation" (lines 361-384) which are potentially more substantial than just a simple excess of events. Furthermore, the Data Mining section defines a "signal" as "any product-event combination with a score exceeding the specified threshold" (line 327). To add to the confusion, the FDA describes a sequence of "signal to potential safety risk to safety risk". Since the Draft Guidance clearly states that investigation of signals is an expectation of sponsors, it is critical that the Agency and sponsors have a clear definition of the term "signal" and that it be used consistently throughout the final guidance.

Data Mining and Signal Detection

While data mining techniques are an emerging tool in post-marketing product surveillance to assist in the early identification of rare adverse events, the application of these techniques is evolving and should be used judiciously. Limitations of the underlying data and data mining techniques must be fully appreciated to avoid false positive causality conclusions. Moreover, since the systematic performance characteristics of these techniques have not been established, data mining techniques should only be considered as a potential supplement to, and not a substitute for, traditional or standard methods of signal detection that utilize clinical and pharmacological judgment and/or decision trees. We recommend that the Agency make it clear within the Guidance that use of data mining techniques is not a mandatory or expected part of signal identification/evaluation. We also request that the Draft Guidance state explicitly that data mining cannot and must not be used to establish a causal relationship between a drug and an event.

International Harmonization of Risk Management Approach

Novartis believes that a global approach to pharmacovigilance and risk management is critical and we strongly encourage FDA to harmonize with international consensus initiatives, including the consistent use of terminology and approach. An example of the current lack of such consistency is the use of the term "Pharmacovigilance Plan" (PVP). The FDA document (line 699) indicates that a PVP should be developed if "routine pharmacovigilance" is not sufficient; that is, a PVP will only be developed when unusual safety signals have been identified, either before or after approval. In contrast, the ICH E2E document states: "For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan." Since both the ICH E2E document and the FDA guidance document are in draft, we strongly urge FDA, as a member of ICH and the E2E Expert Working Group, to harmonize the terminology used in these documents. The final FDA guidance document should incorporate the terminology and definitions agreed to in the final ICH E2E guidance document.

It would also be useful if an explicit cross-reference to the ICH E2E Guidance on Pharmacovigilance Planning was included in Section VII, Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan. This would help clarify how the requirements of the ICH guidance document could be incorporated into a RiskMAP when a RiskMAP is needed, and how a Pharmacovigilance Plan could be developed and submitted in the absence of a RiskMAP.

Assessment of Causality in Individual Safety Reports

As Novartis has also stated in the Draft Guidance on Pre-marketing Risk Assessment, application of causality algorithms to a single case is fraught with misinterpretation. Given the inadequacy of data in individual safety reports, it is almost impossible to rule out with certainty the likelihood that the suspect drug may have contributed to an adverse experience. Most adverse experiences at the individual case report level are assigned a possible association. Therefore, with the exception of cases involving a positive rechallenge, there is little or no advantage in performing causality assessment on individual case reports. Although a series of cases may be used to generate hypotheses concerning the association between an adverse experience and drug exposure, there is no available methodology to date that has been shown to be reliable and reproducible for individual causality assessment. Thus, causality assessment at the individual case level is open to a high likelihood of misinterpretation. We recommend that FDA delete all text suggesting that causality can be determined through assessment of individual safety reports.

Specific Comments

Section: IV.A. Good Reporting Practice

Line(s)	Comment
115 - 118	As stated in our introductory remarks, the definition of pharmacovigilance is not consistent with that proposed in ICH E2E document. While FDA may choose to focus this Guidance on the postapproval period of development, it is not necessary to change the definition. Since FDA is a partner to ICH and a member of the E2E Working group, we recommend that FDA use definitions that have been agreed to internationally. We propose the following revision to this paragraph: "Pharmacovigilance (provide reference to ICH E2E) is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem. This definition encompasses the use of pharmacoepidemiologic studies. For the purposes of this Guidance document, we will focus the discussion on the postapproval period of development and the use of Pharmacoepidemiologic safety studies."

119-120	The goal of pharmacovigilance activities is not to prevent adverse events, but rather to gain additional insight through the gathering of information, which may be helpful to the goal of safe drug use and risk minimization. We recommend modifying this sentence to read: "These activities are undertaken with the goal of identifying these events and understanding to the extent possible, their nature, frequency, and potential risk factors. This information is critical to the goal of minimization and/or prevention of adverse events."
145-147	FDA recommends that sponsors make every attempt to obtain complete information during initial contacts and subsequent follow-up, and encourages sponsors to use trained health care practitioners to query the initial reporters. We suggest that this sentence be clarified to indicate that it applies to serious cases only (as outlined in the March 2003 proposed safety reporting regulations). In addition, it is not appropriate that FDA specify the qualifications of company personnel, but only to state that they must have adequate training, experience, and/or education to perform the required activities. We also suggest that the word "reasonable" be inserted into line 146, so that this sentence reads: "...make every reasonable attempt...".

Section: IV.B. Characteristics of a Good Case Report

Line(s)	Comment
180	We suggest adding the word "relevant", so that this point reads: "Relevant therapeutic measures...".
188-205	The reporting of medication errors and the use of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) taxonomy tool implies that there are specific regulatory reporting requirements for medication errors. To date the most specific guidance from the Agency regarding medication error reporting was in the March 2003 proposed regulations (the "Safety Tome"). Since it is highly unlikely that final regulations regarding medication error reporting will be issued before this guidance document is finalized, we suggest that this section be revised to conform with the current regulations, which require reporting of medication errors only when they also involve an adverse event. We also suggest that the information in lines 196-199 be deleted, as medication errors caused by work environment and personnel are outside of the control of the pharmaceutical industry.

Section: IV.C. Developing a Case Series and Assessing Causality of Individual Case Reports

Line(s)	Comment
243	The use of the term "confounding" in this context may lead to confusion with the epidemiological definition of confounding. We recommend revising the bullet to read: "Absence of an alternative explanation, i.e. no concomitant medications that could cause or contribute to the event; no co- or pre-morbid existing medical conditions."
252-271	The text affirms that for an individual case report, it is rarely possible to assess causality with a "high level of certainty" and that there are "no internationally agreed upon standards or criteria for assessing causality". Further it states that the FDA does not recommend any specific categorization of causality, and that "if a causality assessment is undertaken,...causal categories are specified". From these statements, it would appear that individual case causality assessments are not required, which we support as stated in our General Comments. However, several places in the draft guidance appear to make individual case causality assessments mandatory, including line 283 ("After individual cases are assessed for causality...")

	and line 636 ("...FDA recommends...assess product relatedness at the case level..."). It is important to recognize that individual spontaneous reports cannot truly be assessed for causality; overall trends should be evaluated in aggregate form and hypotheses formed and tested based on the aggregate data. We recommend that the document delete all text suggesting that causality can be determined through assessment of individual safety reports.
255-257	The draft guidance states that "rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with long-term follow-up, are usually needed to assess causality...". Although case-control studies could be employed to examine the association between a drug and an adverse event, or to identify risk factors for an adverse event, they cannot be used to determine causality. We recommend that the document be revised to clarify this statement.
273-279	We suggest that root cause analysis of medication errors by sponsors/applicants be limited to only those causes over which the sponsor/applicant has control (e.g., brand name, labeling and packaging).

Section: IV.E. Use of Data Mining to Identify Product-event Combinations

Line(s)	Comment
313	The statement that data mining methods can be used to provide information on the "characteristics" of a signal is imprecise and could be interpreted to mean that these methods can be used for signal evaluation in addition to signal detection. We suggest that FDA clarify this sentence.
316-317	It must be explicitly stated that data mining is NOT a technique that can be used to make causal attributions between products and adverse events. Data mining is a hypothesis-generating tool, not a technique for attributing causality. As acknowledged in the sentence preceding line 316, data mining may be able to identify unusual or unexpected product-event combinations warranting further investigations. We propose that the sentence in line 316-317 be replaced with the following: "Historically, identifying potential drug-event associations of interest has utilized a variety of judgments, rules, and/or decision trees based on sound clinical/pharmacological judgment. Data mining is an additional technique that may have value as a supplement to, but not as a substitute for, existing signal detection strategies."
319 - 320	We suggest that the term "rate" should be avoided in the context of spontaneous reports, since it may lead to confusion with the epidemiologic definition of rate (i.e. quantification of the frequency of an event in a population per unit of time). If used, it should be specified as "reporting rates" (e.g., "observed reporting rate", "expected reporting rate"). In addition, there seems to be a lack of consistency in the use of the terms "events" and "reports". The document describes comparing "the fraction of all events reported for a particular product .....with the fraction of reports for all drugs that are for the same event". In this context, it should be clearly defined whether the unit of analysis is events or reports (individual cases).
321	We suggest that the word "corrected" be changed to "stratified".
325-353	The statistical validity of the available data mining tools has not yet been established. The draft guidance document makes reference to thresholds, sensitivity and specificity, which overstates the capabilities of these tools at the current time. Moreover, terms such as "true effect" and "false positive" imply that there is an accepted standard against which to make a comparison. There still exists a great deal of uncertainty about the predictive value, sensitivity, and specificity of data mining tools, and additional developmental work is needed;

329	We suggest revising this to read "...potential signals...".
333	The draft guidance states that several data mining methods are worth considering. We suggest that it is still debatable whether data mining is worth considering, due to false positive, false negative, limitations of the data, and lack of gold standard.
335-336	The full name and reference for the Bayesian method is "Bayesian Confidence Propagation Neural Network" (BCPNN) (Bate, 1998). We are unaware of any statistical proof that the cut-off point for "small" is 20, and recommend that the Agency include a reference to show that, empirically, small means less than 20.
337	We suggest that "adverse events" be modified to "adverse event reporting" or the equivalent, so that this sentence reads: "...may provide insights into the patterns of adverse events reported for a given product..."
340-342	We suggest also adding co-morbidities and numerous potential unmeasured/ unrecorded confounders as potential biases. We believe that just noting the underlying disease and concomitant medication underestimates/underemphasizes the problems and limitations that are inherent to voluntary reporting systems.
347-349	Consideration of signals that exceed a specified threshold can apply to both traditional methods and computational algorithms. A careful assessment of all information should be performed following identification of a signal derived from any method, not just data mining. We suggest that the language be modified to reflect this concept.

Section: IV.F. Safety Signals that May Warrant Further Investigation

Line(s)	Comment
361	We suggest changing the word "typically" to "may", so that this sentence begins: "Safety signals that may warrant further investigation...".
368	We request that FDA provide clarification on the definition of "more than a small number of serious events thought to be extremely rare".
375	FDA seems to be inserting the idea of "potential" medication errors into this guidance document as a consideration of a "safety signal that may warrant further investigation". This is not an accepted term, nor is a guidance document the appropriate place to attempt to effect changes in existing regulatory requirements. We request that any mention of potential medication errors be deleted from the guidance document until this concept is codified into regulation.

Section: IV.G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

Line(s)	Comment
406	Suggest adding the word "specific" so that the sentence ends "...are not available for the specific population of interest".
408-423	We question why FDA recommends calculating crude reporting rates given their recognized unreliability and potential for misleading conclusions. If a reporting rate is large enough to warrant further investigation, an investigation utilizing other (i.e., not spontaneous reports) databases or studies is needed. In addition, reporting rates differ dramatically during the product lifecycle. We request that FDA clarify how these crude reporting rates will be used in the assessment of the benefit to risk balance and how the variation in reporting rates over the product's life-cycle should be taken into account.
410-412	We question whether the requirement to include only US cases and US exposure data in the analyses indicates that FDA is not interested in analyses involving global

	data. Sponsors frequently perform their analyses of safety using fully integrated global datasets, which provides a more accurate reflection of the global product profile. In addition, it is often not feasible to provide an estimate of national patient exposure. We do not routinely have access to patient-level data. The available data that most accurately reflects patient use is prescription data. We suggest that the guidance document incorporate the same guidance for estimating exposure as outlined in the CIOMS V document, namely: • total quantity sold (e.g., kg, liters) • # of packages sold (e.g., boxes, bottles) • # of units sold (e.g. tablets, vials) • # of prescriptions or treatments • # of patients • person-time: treatment-months, person-months, person-years (incidence density) • Defined Daily Dose (DDD) Selecting the unit for the reporting rates should be determined on a case-by-case basis. For chronic diseases, person-years are commonly used to describe exposures. For infectious diseases, # of prescriptions may be more appropriate. The DDD is a suggested standard unit by the WHO for assessing market penetration of a drug and for making comparisons between countries. In non-U.S. countries, the patient-level estimates are seldom available.
408 - 418	The reporting of adverse events can also be influenced by temporal trends, such as calendar time, publicity, and surveillance and market size effects. Due to these factors, analysis of temporal trends may also be useful in interpretation of the data. As the text is currently written, calculation of only total reporting rates is suggested. There is no consideration given to the relevance of temporal trends analysis. We suggest that lines 417 – 418 be revised to read: "Comparisons of reporting rates and their temporal trends can be valuable, ...".

Section: V.A. Pharmacoepidemiologic Safety Studies

Line(s)	Comment
465	We strongly support the use of pharmacoepidemiologic "nonrandomized observational studies of patients in the real world" to characterize, clarify or validate safety signals for pre and/or post-marketed drug products. However, the regulatory reporting of adverse events reported in these types of studies, specifically, expedited and/or periodic adverse event reporting, is unclear. The draft ICH E2D and Safety Tome, and CIOMS V documents state that any organized attempt to collect data in the post-marketing environment should be categorized as "solicited data". We interpret this to mean that data from pharmacoepidemiologic studies would be categorized as solicited, and would be reported in accord with the post-marketing regulations for expedited and periodic study reporting. We request clarification regarding whether these data should also be included in an IND Annual Report. In addition, regardless of how these data are reported, we request clarification regarding whether they should be segregated from mainstream pre- and post-marketing periodic reports.
481-491	Although we agree that pharmacoepidemiology studies offer advantages over controlled trials when assessing uncommon or delayed adverse events, in the setting of a very rare event, pharmacoepidemiology studies also have limitations and may not have the power to detect differences in rates. It is also important to understand that such studies do not provide early signal detection or real time data. It typically takes years of observational research to confirm or refute a potential

	signal.
485-487	We suggest deleting the words "where the main difficulty is that they", so that this sentence reads "On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients...".
489-493	This paragraph states that observational studies are more prone to confounding and effect modification and other bias and potentially more difficult to interpret than clinical trials. This is not always true as long as observational studies are designed, performed, and analyzed appropriately. Inappropriate randomization in clinical trials will result in serious bias. In addition, there are methods to adjust for confounders, effect modifiers and other bias in observational studies. As noted above, it is important to be aware of the strengths and limitations of observational studies as well as those of clinical trials.
509-510	We do not disagree that pharmacoepidemiologic studies are subject to bias and confounding. However, clinical trials, particularly long term studies, are also subject to an array of biases that can lead to difficulties in interpreting results. We suggest that a statement about the limitations of clinical trials be added here.
511	While we agree that it is desirable to conduct more than one study, this is frequently not feasible. In the setting of a rare or very rare event, and the need for medical records to validate the data, there are often very limited options for conducting even a single safety study.
526	Not all studies are hypothesis driven, and thus, may not need power calculations.
530-551	It would be helpful if FDA acknowledge and provide guidance on the use of non-US automated databases, which are increasingly available. Further, since the use of automated databases will not be feasible for studying all safety risks, the Agency should provide guidance on primary data collection methods, including the use of publicly- or privately-funded cohort studies already collecting data in the US and Europe (e.g., NHANES, EuroSCAR).
553	We support the statement on the desirability of validation in automated database studies, although it should be noted that circumstances such as medical data privacy legislation may significantly inhibit these efforts.

Section: V.B. Registries

Line(s)	Comment
Footnotes 14 and 15	Reference 14 should probably be "ibid", rather than "Id". Reference 15 appears to be the same as reference 12.
564-569	The definition given for a registry does not clearly distinguish an observational study from a registry. It appears that an observational study always has a control group and a well-defined hypothesis, whereas a registry has only treated patients and an objective, but no *a priori* hypothesis. The CIOMS V Working Group recommended that the term "registry" be reserved for inventories of case information collected without an *a priori* research hypothesis, but held in reserve for future possible study and analysis. If this recommendation were included in the definition of registry, it would help to clarify the difference between a registry and an observational study.
571 - 572	The term "follow-up" in this sentence could be misunderstood to mean that follow-up information could be sought through the creation of registries. We suggest that the term "follow-up" be replaced with either "specifically address" or "evaluate".

Section: V.C. Surveys

Line(s)	Comment

625-626	This sentence recommends "...validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers". Not all surveys require validation of this nature; for example, how would one validate a survey for patient knowledge of label, sound-alike or look-alike trade names, etc?

Section: VI. Interpreting Safety Signals: from Signal to Potential Safety Risk

Line(s)	Comment
637	As noted in our comments regarding case level causality assessment above (lines 252-271) and in the General Comments, we do not believe that this should be a requirement. Given the inadequacy of data in individual safety reports, it is almost impossible to rule out with certainty the likelihood that the suspect drug may have contributed to an adverse experience. Most adverse experiences at the individual case report level are assigned a possible association. Therefore, with the exception of cases involving a positive rechallenge, there is little or no advantage in performing causality assessment on individual case reports. Although a series of cases may be used to generate hypotheses concerning the association between an adverse experience and drug exposure, there is no available methodology to date that has been shown to be reliable and reproducible for individual causality assessment. Thus, causality assessment at the individual case level is open to a high likelihood of misinterpretation. We recommend that FDA delete all text suggesting that causality can be determined through assessment of individual safety reports.
645	We suggest that the word "relevant" be inserted into this sentence, so that it reads: "...submit a synthesis of all relevant available safety information...".
654-663	We suggest that the following be added to the list of information that could be evaluated to assess the degree of causality between use of a product and an adverse event: Background rates in general and specific patient population, if available;
667	This section appears to indicate that further investigation of the signal through additional studies is always required. This may not be the case in every situation (e.g., it might be sufficient to change the product's label). We suggest that the document be revised to clarify this point.
669-672	We propose that the guidance state that once FDA has completed its own assessment of the potential safety risk, it will share its conclusions with the sponsor/applicant.

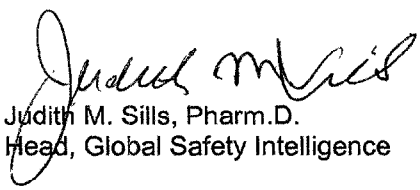
Section: VII. Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan

Line(s)	Comment
699-741	The draft guidance states that pharmacovigilance plans may be appropriate for products that have "safety signals" identified pre- or post-approval. Again, the use of the term "signal" is confusing here and perhaps it would be clearer to use the term "safety risk" instead of "safety signal".
718	The statement regarding the frequency with which the event occurs is vague and requires clarification. "Frequency" means the number of cases. The number of population at risk (denominator) is needed to calculate incidence of risk.
742	It is not clear how the third category (other significant safety concerns exist) differs from the first category (safety signals have been identified pre- or post-approval). Again this may be due to the confusion around the definition of safety signal.

748	Suggest that this be revised to state: "Submission of specified serious expected adverse event reports in an expedited manner beyond routine required reporting", as serious unexpected adverse events are routinely submitted as expedited reports.
756-761	We recommend that the document include a definition of "active surveillance". It is unclear how the databases mentioned in this section may provide active surveillance.

If you have any questions regarding this document, please contact Dr. Judith Sills at (862) 778-2472.

Sincerely,



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